Pending Claims

Prior to this Amendment, Claims 21-37 were pending. By this Amendment, claims 26, 32, and 34 are cancelled without prejudice. (Claims 26 and 32 would essentially be redundant in view of Amendments to Claims 21 and 28.) Claims 38-40 have been added.

As a result, the pending claims are Claims 21-25, 27-31, 33, and 35-40.

Support for amendments

Support for the amendments to Claim 21, specifying two subpopulations of microparticles, each subpopulation population with a different antigen, is found in Example 7.

Support for the amendments to Claim 28, specifying two subpopulations of microparticles, each subpopulation population with a different antigen, is found in Example 8.

Support for the amendment to Claim 36, specifying a T_H2 - polarized protective immune response, is found in Example 8 (e.g., p. 23 , lines 12-13).

Rejections of Claims 21,22, and 28 under 35 U.S.C. 103(a) in light of Andrianov *et al.* U.S. Pat. No. 5,807,757 (Paragraph 3 of the Office Action)

The Examiner has rejected Claims 21, 22 and 28 as being unpatentable over Andrianov *et al.* U.S. Pat. No. 5,807,757. This rejection is respectfully traversed on the

following grounds:

Applicant has amended Claims 21 and 28. Claim 22 is dependent on Claim 21. All three claims are now "method" claims and comprise the oral administration of two subpopulations of particles, the antigen in the particles of one subpopulation differing from the antigen in the particles of the other subpopulation. The "coacervate" limitation has been removed although it is present in new dependent claims.

In view of the history of this case, and particularly taking into account that the amended Claims 21, 22, and 28 each deal with two subpopulations of particles, Applicant believes that the Examiner would consider the following references as pertinent to those amended Claims: Singh et al (Vaccine, 1998), O'Hagan et al (U.S. Patent 5,603,960), Shahin et al. (Infect. Immunol., 1995, 63(4):1195-1200). These references are referred to below as Singh (Vaccine, 1998), O'Hagan, and Shahin, respectively.

Singh (Vaccine, 1998) disclosed poor results when administering, apparently by intramuscular injection, microparticles loaded with 2 different antigens. Consistent with those poor results, the Examiner noted the following in the Office Action of May 11, 2000 (see page 5):

> It is disclosed that more potent antibody responses were induced with a single antigen in the microparticles rather than with two antigens in the same microparticles (page350, column 2). It is disclosed that it was previously reported that one antigen in a multi-component vaccine may result in reduced immunogenicity for all the antigens (page 350, column 2).

Shahin disclosed successful results when administering a mixture of microparticle subpopulations intranasally, the subpopulations differing as to the antigen in their microparticles. Shahin does not report having orally administered mixed subpopulations of microparticles. Indeed, Shahin generally had poor success with oral administration, stating that oral immunization with microencapsulated FHA failed to consistently elicit detectable specific antibodies in the serum, gut, or lung secretions. (See page 1199, right column, second paragraph, first 4 lines) and, more strongly, that there was a failure to induce a protective mucosal response via the oral route (page 1199, second paragraph, line 12ff).

Singh and Shahin are the two references that deal most directly with mixed subpopulations. It can be seen that, taken together, they provide no motivation to pursue oral administration of a mixture of subpopulations, each subpopulation carrying a different antigen. The lack of motivation is even more evident for nanoparticles (no mixed subpopulation data reported for any route) than for microparticles.

O'Hagan and Andrianov have less relevance than Singh and Shahin as regards the present rejection.

O'Hagan was cited in the Office Action of February 5, 2001 as disclosing the oral administration of antigen-containing microparticles sized between 100 nm and 10 um and having been made by a solvent-evaporation method. (See page 5 of the Office Action dated February 5, 2001). O'Hagan does not, however, disclose the size of the particles that were used to obtain the immunological data. In any case, O'Hagan does not supply data on the use of mixtures of particle subpopulations.

Andrianov appears to have been cited by the Examiner primarily to address the

coacervate limitation in the claims. Because the coacervate limitation has been removed from Claims 21, 22 and 28, Andrianov is presumably now less pertinent than the references discussed above. Nevertheless, Applicant notes for the record that the coacervate particles that Andrianov made are exclusively microparticles (See for example Figures 3, 6, and 7) and that Andrianov has no immunization data.

In summary, the prior art does not provide motivation to use combinations of subpopulations, each subpopulation with a different antigen, in an orally administered vaccine, as in Applicant's Claims 21, 22 and 28.

Rejections of Claims 24-28, 30-34 and 36 under 35 U.S.C. 103(a) in light of Andrianov *et al.* U.S. Pat. No. 5,807,757 and in view of Jones and Shahin *et al* (Infect. Immunol., 1995, 63(4): 1195-1200) (Paragraph 4 of the Office Action).

The Examiner has rejected Claims 24-28, 30-34 and 36 under 35 U.S.C. 103(a) in light of Andrianov *et al.* U.S. Pat. No. 5,807,757 and in view of Jones and Shahin *et al* (Infect. Immunol., 1995, 63(4): 1195-1200). Claims 26, 32 and 34 have been cancelled. As to the remaining pending claims, this rejection is respectfully traversed on the following grounds:

With the exception of Claim 36, all the claims pertinent to this rejection are Claims that are directly or indirectly dependent on independent claims 21 and 28. Applicant believes, for reasons set forth herein, that the independent claims are patentable over the prior art, which would imply that their dependent claims are also patentable over the prior art. This does not preclude that there may be additional reasons why individual dependent claims are patentable over the prior art.

Claim 36, as a result of the amendments herein, is now specifically limited to the induction a T_H2-polarized protective immune response against *B. pertussis* by antigen-loaded nanoparticles. None of the prior art cited by the Examiner would make these claims obvious.

Rejections of Claims 23, 29, 35 and 37 under 35 U.S.C. 103(a) in light of Andrianov *et al.* U.S. Pat. No. 5,807,757 and Singh *et al* (Adv. Drug Delivery Reviews) (Paragraph 5 of the Office Action)

All 4 rejected claims are directly or independently dependent on independent claims 21, 28, and 36. Applicant believes, for reasons set forth herein that the independent claims are patentable over the prior art, which would imply that their dependent claims are also patentable over the prior art. This does not preclude that there may be additional reasons why individual dependent claims are patentable over the prior art.

In view of the foregoing remarks, it is respectfully submitted that all of the claims now remaining in this application are allowable and such favorable action is respectfully requested.

Respectfully submitted,
CAESAR, RIVISE, BERNSTEIN,
COHEN & POKOTILOW, LTD.

February 14, 2002

By Allan H. Fried
Allan H. Fried

VERSION WITH MARKINGS TO SHOW CHANGES MADE

21. (Amended) A [vaccine formulation for oral administration comprising: a] method of inducing a protective immune response, said method comprising orally administering to a subject therapeutically effective [amount of a coacervate, the coacervate comprising microparticles] amounts of at least a first and a second subpopulation of microparticles [one antigen and a biocompatible, biodegradable polymer], wherein each microparticle comprises an antigen [at least one antigen is] entrapped or encapsulated by [the] a biocompatible, biodegradable polymer, and wherein the antigen in the microparticles of one subpopulation is different than the antigen in the microparticles of the second subpopulation and at least 50% of the microparticles are less than 5μm[; and

a pharmaceutically acceptable carrier].

22. (Amended) The [formulation] method of claim 21 wherein the microparticles are sized such that at least 50% of the microparticles are less than 3 μm.

23. (Amended) The [formulation] method of claim 21 wherein the biocompatible, biodegradable polymer comprises a copolymer of lactic acid or an enantiomer of lactic acid with glycolic acid or an enantiomer of glycolic acid.

24. (Amended) The [formulation] method of claim 21 wherein the [at least one antigen comprises] antigen in the first subpopulation of microparticles is a *B. pertussis* antigen and the antigen in the first subpopulation of microparticles is a *B. pertussis* antigen.

25. (Amended) The [formulation] method of claim 24 wherein the *B. pertussis* [antigen is] antigens are selected from the group consisting of inactivated pertussis toxin (PTd), filamentous hemaglutinin (FHA) and pertactin.

27. (Amended) The [formulation] method of claim 21 [26] wherein [each of the antigens is] both the antigen in the first subpopulation of microparticles and the antigen in the second subpopulation of microparticles are selected from the group consisting of inactivated pertussis toxin (PTd), filamentous hemaglutinin (FHA) and pertactin.

28. (Amended) A [vaccine formulation for oral administration comprising: a] method of inducing a protective immune response, said method comprising orally administering to a subject therapeutically effective [amount of a coacervate, the coacervate comprising nanoparticles] amounts of at least [two subpopulations] a first and a second subpopulation of nanoparticles [one antigen and a biocompatible, biodegradable polymer], wherein each of said nanoparticles comprises an antigen [at least one antigen is] entrapped or encapsulated by [the] a biocompatible, biodegradable polymer, and wherein the antigen in the nanoparticles of one subpopulation is different

than the antigen in the nanoparticles of the second subpopulation and at least 50% of the nanoparticles are less than 600 nm[; and

a pharmaceutically acceptable carrier].

29. (Amended) The [formulation] method of claim 28 wherein the biocompatible, biodegradable polymer comprises a copolymer of lactic acid or an enantiomer of lactic acid with glycolic acid or an enantiomer of glycolic acid.

30. (Amended) The [formulation] method of claim 28 wherein the [at least one antigen comprises] antigen in the first subpopulation of microparticles is a *B. pertussis* antigen and the antigen in the first subpopulation of microparticles is a *B. pertussis* antigen.

31. (Amended) The [formulation] method of claim 30 wherein the *B. pertussis* antigen is selected from the group consisting of inactivated pertussis toxin (PTd), filamentous hemaglutinin (FHA) and pertactin.

33. (Amended) The [formulation] method of claim 28 wherein [each of the antigens] both the antigen in the first subpopulation of microparticles and the antigen in the second subpopulation of microparticles is selected from the group consisting of inactivated pertussis toxin (PTd), filamentous hemaglutinin (FHA) and pertactin.

35. (Amended) The [formulation] method of claim 34 wherein the biocompatible, biodegradable polymer comprises a copolymer of lactic acid or an enantiomer of lactic acid with glycolic acid or an enantiomer of glycolic acid.

36. (Amended) A method of inducing a T_H2-polarized protective immune response against *B. pertussis*, comprising orally administering to a subject a pharmaceutically effective amount of [a coacervate, the coacervate comprising] nanoparticles sized such that at least 50% of the nanoparticles are less than 600nm, the nanoparticles comprising at least one *B. pertussis* antigen selected from the group consisting of inactivated pertussis toxin (PTd), filmentous hemaglutinin (FHA) and pertactin, said antigen entrapped or encapsulated by a biocompatible, biodegradable polymer.

37. (Amended) The [formulation] method of claim 36 wherein the biocompatible, biodegradable polymer comprises a copolymer of lactic acid or an enantiomer of lactic acid with glycolic acid or an enantiomer of glycolic acid.

CERTIFICATE OF MAILING

I hereby certify that the foregoing AMENDMENT, a Transmittal Letter, and a Petition for Extension of TIme, re Application Serial No. 09/386,709 are being deposited with the United States Postal Service as first class mail, postage prepaid, in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231 on this 14th day of February, 2002.

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Reg. No. 31,253